DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223

December 27, 2002

WARNING LETTER
SJN-03-06

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Jaime L. Albors
General Manager
Searle, Ltd.
PO Box 11247
Barceloneta, PR 00617

Dear Mr. Albors:

On September 9, 2002 through September 18, 2002, the Food and Drug Administration conducted an inspection of your prescription drug manufacturing facility, Searle, located at Road #2, Km 64.4, Barceloneta, PR 00617. Our evaluation of the inspection report, FDA 483, Exhibits, and your response, dated October 15, 2002, revealed that the pharmaceutical products manufactured by your facility are adulterated within the meaning of section 501(a) (2) (B) of the Federal Food, Drug and Cosmetic Act because they were not manufactured in accordance with current Good Manufacturing Practices (cGMP) as defined in 21, Code of Federal Regulations (CFR), Part 211.

The cGMP deviations documented during the inspection include:

1. Failure of your Quality Control unit to exert its responsibility and authority as required by 21 CFR 211.22 (a),(c) in the following:

   a. Plaquenil 200 mg, and Winstrol 2mg tablets are not monitored for related substances and/or degradation products prior to their release for distribution as required by 21 CFR 211.165 (a).

   b. Plaquenil 200 mg, and Winstrol 2mg tablets are not monitored for impurities and/or degradation products during stability studies to assure that the quality of your products has not been affected as required by 21 CFR 211.166 (a).

For example:

According to some records reviewed during the inspection, you developed a stability indicating method in 1981 for Winstrol and in 1988 for Plaquenil capable of detecting degradation products. However, neither of the methods have been used for this even though you have data to show that degradation products and/or impurities can elute at long retention times. Both aforementioned methods are only used for assay determination with a limited run time of 9 minutes.

c. Failure to have specifications for any known or unknown impurities and/or degradation products that maybe present in Plaquenil and Winstrol tablets, respectively, as required by 21 CFR 211.160 (a), (b).

2. Failure to implement in a timely manner a HPLC method for the determination of impurities in Omnipaque injection as required by 21 CFR 211.160 (b). The method was developed in 1992, and it was not until 2/4/02 that it was submitted to FDA as CBE-30 supplement. You still have not implemented the HPLC method and you are currently relying on a [redacted] method, which is not as accurate and sensitive as the HPLC method, to monitor the impurities at the time of release and during stability studies.

3. Failure to have adequate in-process controls for the manufacturing process of Plaquenil and Winstrol tablets as required by 21 CFR 211.110 (a) and (b).
For example:

(a) During the validation of the manufacturing process for Plaquenil, two of the validation lots (# [redacted] and [redacted] had out of specification results for the hardness test [redacted] However, in your validation report you concluded that lots # [redacted] and [redacted] were in compliance because low hardness result tablets pass friability and high hardness result tablets pass dissolution testing. You are also accepting hardness results outside your established specifications for routine manufacturing process.

During the review of the records collected by the investigator we also noticed that no in-process testing (weight, hardness, friability and thickness) were performed for the validation lot # [redacted] of Plaquenil tablets due to "a lack of sampling coordination". Please include in your response the corrective actions taken to address this issue.

(b) Winstrol tablets do not have an officially established specification for thickness. Routine manufacturing batches are manufactured with a "to be determined thickness specification".

(c) During the performance qualification of Winstrol tablets, using a new supplier of drug substance, the three validation lots [redacted] had out of specification results for the hardness test ([redacted]). However, in your validation report you concluded that the three lots were in compliance because low hardness results pass friability and high hardness results pass dissolution test. In addition, a fourth validation lot ([redacted]) was manufactured using a different specification for hardness [redacted]. You have failed to demonstrate the consistency of your manufacturing process, because the new hardness specifications have not been assessed with the manufacture of three consecutive batches.

4. Failure to follow your procedure related to your Change Control Program as required by 21 CFR 211.100(a). For example, many instances were reported as lacking the required signatures prior to the implementation of a change requested.

We acknowledge the receipt of your response letter dated October 15, 2002. Even though you indicated that you decided to stop the manufacture of Plaquenil and Winstrol tablets, you do not mention any actions being considered regarding any batches of products that may be currently on the market and for which, impurities and/or degradation products were not monitored.

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to promptly correct these deviations may result in regulatory action without further notice. These sanctions include, but are not limited to, seizure and/or injunction.

Please notify the San Juan District office in writing, within 15 working days of receipt of this letter, of your corrections to the violations identified in this letter. Corrective actions addressed in your previous letter may be referenced in your response to this letter as appropriate.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Avenue, San Juan, Puerto Rico 00901-3223, Attention: Margarita Santiago, Acting Compliance Officer.

Sincerely,

Donald M. Watchko
Acting District Director